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Trial Exhibit

Purdue et al. v. Endo et al.
Nos. 00 Civ. 8029 (SHS),
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DX 2766

Steady-State Pharmacokinetics of Controlled Release Oral Morphine Sulphate in Healthy Subjects

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Summary

The pharmacokinetics of oral morphine sulphate as controlled release tablets ('MS-Contin') and solution were compared at steady-state. Plasma morphine concentrations were determined over 24 hours following the last dose of each drug when given in a randomised, crossover fashion to healthy subjects. Radioimmunoassay was used, which was sensitive yet provided good specificity relative to high-performance liquid chromatography. Controlled release tablets had 86% the bioavailability of the solution. Although each dose of controlled release tablets was double that of the solution, their peak plasma concentrations were the same. Time to maximum concentration was 3 times longer for controlled release tablets with an absorption half-life twice that of the solution. Elimination of both drugs was similar and biphasic with the minor terminal portion at 10 times the half-life of the major early process. These data explain the analgesic duration of 12 hours observed in clinical studies and the lack of accumulation with morphine compared with methadone.

Controlled release oral morphine sulphate tablets offer the clinical advantage of less frequent dosing, with an attendant increase in quality of life for patients with chronic pain requiring repeated-dose opioid analgesia. The pharmacokinetic literature on controlled release morphine sulphate comprises only a small number of limited studies. According to Vater et al. (1984) no statistical correlation was found between blood concentrations following a 20mg dose of controlled release morphine sulphate, and analgesia using an artificial tourniquet pain model. Few pharmacokinetic parameters were derived for the controlled release preparation over the 7 hours of study, but a C_{max} of 14.8 $\mu\text{g/L}$, t_{max} of 2.4 hours and an elimination half-life of 4.1 hours determined by high-performance liquid chromatography (HPLC) were reported. No comparison against a reference mor-

phine preparation was made. Welsh et al. (1983) compared controlled release morphine sulphate with morphine sulphate solution. Limited morphine pharmacokinetic data from radioimmunoassay (RIA) were derived from this 8-hour study, including C_{max} and t_{max} of 55.0 $\mu\text{g/L}$, 3.3 hours and 73.1 $\mu\text{g/L}$, 2.9 hours for tablets and solution, respectively. Also, the tablets were shown to have 86% of the bioavailability of the solution. Leslie et al. (1980) employed gas-liquid chromatography (GLC) to demonstrate sustained morphine plasma concentrations in normal subjects given controlled release compared with immediate-release morphine sulphate, although no pharmacokinetic parameters were calculated.

In addition, there are only a limited number of reports on the pharmacokinetics of oral morphine in general. Representative are several studies such

as Säwe et al. (1983) who reported steady-state kinetics of oral morphine in cancer patients. Parameters were based on a maximum of 6 hours data post-dosing using a GLC morphine assay. The HPLC assay developed by Svensson et al. (1982) was reported to measure morphine and its glucuronide metabolites. Following regular 4-hourly dosing with oral morphine hydrochloride 100mg, plasma samples were assayed only up to 4 hours post-dose. Morphine concentrations peaked by 0.5 hours and declined rapidly thereafter, while the glucuronide metabolite concentrations were many times higher and did not appear to decrease at the same rate as that of the parent molecule. Brunk and Delle (1974), using a radioisotope technique, assayed plasma morphine and extractable morphine metabolites, presumably the glucuronides, and derived some kinetic parameters. By 9 hours after a single 10mg oral dose of morphine sulphate, the parent molecule could not be detected in the plasma, whereas metabolites were still present at 24 hours post-dose. However, Stanski et al. (1978) using RIA found residual plasma morphine 24 hours after morphine sulphate 10mg given by rapid intravenous infusion. Pharmacokinetic calculations were not conducted on the post-12-hour data due to lack of confidence in the specificity of the assay.

The purpose of this study was to determine the pharmacokinetics of oral controlled release morphine sulphate given as 'MS Contin' (marketed in Europe as 'MST Continus Tablets') compared with oral morphine sulphate solution.

Methods

Healthy subjects, rather than cancer patients, were used in order to obtain less variable pharmacokinetic parameters. They were free from significant abnormal medical findings, including liver and kidney disease, and had no history of drug abuse. Medications were not used by these subjects during the week prior to the study and urine spot tests for street drugs were negative.

Subjects were domiciled in the clinic for the entire study period and gave written informed consent to a protocol which had the approval of a duly constituted Institutional Review Board. The protocol design was a repeated dose, randomised, crossover study. Subjects were administered either 30mg controlled release morphine sulphate tablets orally every 12 hours for 3 days or 15mg morphine sulphate solution orally every 6 hours for 3 days. Crossover to the alternate drug occurred on study day 5, with blood sampling performed on the fourth day of each study arm. Plasma was obtained from blood drawn for trough values on the 2 days prior to the sampling days and on the fourth day of each phase at 0.25, 0.5, 1, 1.5, 2, 3, 6, 8, 10, 12, and 24 hours after dosing.

Plasma was separated from the whole blood samples and frozen until the time of assay. Morphine concentrations were determined by radioimmunoassay (Matejczyk et al. 1985) modified by Hazelton Laboratories America, Inc., Madison, Wisconsin for plasma determination sensitive to 0.13 µg/L with a coefficient of variation of 13.0%

Table II. Steady-state parameters

Parameter (n = 13)
AUC ₀₋₁₂ (µg/L · h)
Relative bioavailability (area ratio adjusted for dose)
C _{max} (µg/L)
t _{max} (h)
t _{1/2} (h) apparent
t _{1/2} (h) apparent
t _{1/2} (h) apparent

Abbreviations: AUC = area under the curve; t_{1/2} = elimination half-life; t_{1/2} = phase.

at concentrations between 1 and 2% of the reactivity with morphine. A second RIA was tried which was reliable, but resulted in plasma morphine concentrations an order of magnitude lower than those reported by Catlin (1981). To ensure the specificity of the assay, a number of samples were assayed for morphine by HPLC having no cross-reactivity with morphine-3-glucuronide, although RIA. 80 plasma samples were assayed by the two techniques. Linear regression on the log-log plot revealed a correlation coefficient of 0.92, a slope of 0.62, and a sample range from 1 to 100 ng/ml. The plasma morphine concentrations determined by RIA in this work were in good agreement with the values obtained by HPLC.

Table I. Daily morphine trough concentrations (mean ± SE) for controlled release tablets (MSC) and solution (MSS), in healthy subjects

Formulation	Concentration prior to serial sampling (µg/L)		Concentrations on day of serial sampling (µg/L)	
	2 days	1 day	first trough	second trough
MSS (15mg every 6h)	6.1 ± 0.3	5.9 ± 0.8	7.7 ± 0.8	6.5 ± 0.5
MSC (30mg every 12h)	2.9 ± 0.3	5.4 ± 0.8	5.4 ± 0.5	4.8 ± 0.7

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Table II. Steady-state pharmacokinetics of oral morphine formulations in healthy subjects

Parameter (n = 13)	Morphine sulphate solution 15mg	Controlled release morphine tablet 30mg	Significance
AUC ₀₋₁₂ (µg/L · h)	71.8 ± 2.5	122.8 ± 3.6	p < 0.001
Relative bioavailability (area ratio adjusted for dose)	100%	86% (range 69 to 118%)	
C _{max} (µg/L)	22.0 ± 1.0	20.3 ± 1.0	p > 0.05
t _{max} (h)	0.77 ± 0.24	2.27 ± 0.24	p < 0.001
t _{1/2α} (h) (apparent)	0.45 ± 0.13	0.81 ± 0.11	p < 0.05
t _{1/2β} (h) (apparent)	3.52 ± 0.16	3.62 ± 0.04	p > 0.05
t _{1/2γ} (h) (apparent)	45.6 ± 31.0	37.8 ± 3.4	p > 0.05

Abbreviations: AUC = area under the concentration-time curve; C_{max} = peak plasma concentration; t_{max} = time to C_{max}; t_{1/2α} = apparent absorption half-life; t_{1/2β} = elimination half-life for the first elimination phase; t_{1/2γ} = elimination half-life for the second elimination phase.

ancer patients, variable pharmacokinetics free from significant liver disease, history of drug abuse, and urine spot

indic for the enrollment of a duly informed consent. The protocol was randomised, double-blind, and patients received either morphine sulphate tablets or controlled release morphine tablets for 3 days. Blood samples were obtained from patients on the fourth day of each 2 days prior to the first day of each 0, 12, and 24

whole blood assay. Morphine was modified by radioimmunoassay. Madison, sensitive to a concentration of 13.0%

ISS), in healthy

of serial

second trough

5 ± 0.5

8 ± 0.7

at concentrations between 1 and 32 µg/L. Cross-reactivity with morphine-3-glucuronide was less than 2%. A second RIA assay (Moore et al. 1984) was tried which was reported to be equally as reliable, but resulted in plasma morphine concentrations an order of magnitude higher than the former assay. This discrepancy in the magnitude of plasma morphine concentrations is a phenomenon previously reported (Catlin 1977; Grabinski et al. 1983). To ensure the specificity of the RIA used in this study, a number of subject plasma samples were assayed for morphine from both formulations by HPLC having no cross-reactivity with morphine-3-glucuronide, although lacking the sensitivity of RIA. 80 plasma samples obtained from a previous study were assayed by these RIA and HPLC techniques. Linear regression (HPLC on y-axis and RIA on x-axis) revealed a correlation of 0.85, p < 0.001, a slope of 0.62, and an intercept of 0.77 given a sample range from 1 to 25 µg/L. Thus, in general, the plasma morphine concentrations determined by RIA in this work when multiplied by 0.6 would yield values comparable to HPLC assay. For ex-

ample, a value of 8 µg/L by RIA would correspond to 5 µg/L by HPLC; these were, in fact, approximately the mean values observed in this study. The predictability of absolute values (HPLC) of morphine from RIA values allowed meaningful morphine determinations at the limit of HPLC sensitivity. While values of the study RIA were correlated with and fractionally higher than those assayed by HPLC, interestingly the other RIA (Moore et al. 1984) yielded values 10 times higher, presumably due to significant cross-reacting metabolites of morphine.

Statistical significance of the mean difference was determined by Student's paired t-test.

Results

The 13 subjects evaluated had a mean age of 32 years (range 20 to 41 years) and weighed 72kg (range 59 to 81kg). The treatment crossover was balanced with 7 participants on one study arm and 6 on the other. Attainment of steady-state was confirmed by measurement of comparable plasma morphine

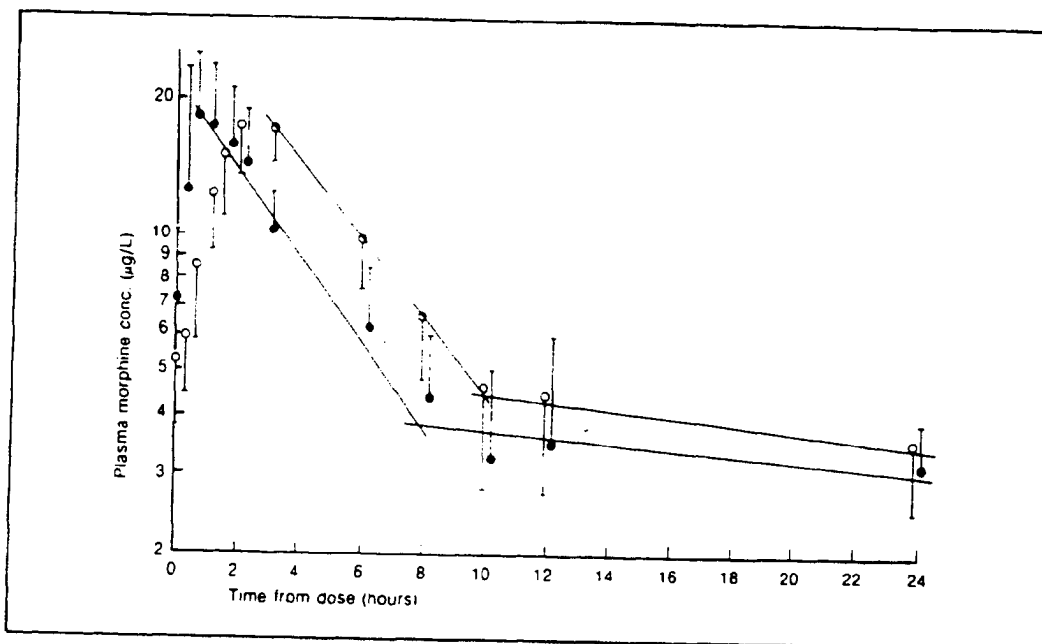


Fig. 1. Log mean ($n = 13$) plasma morphine concentration (log scale) versus time curves for 2 oral morphine formulations, one a controlled release morphine sulphate tablet ('MS Contin') (O) 32mg every 12 hours for 3 days and the other morphine sulphate solution (●) 15mg every 6 hours for 3 days. The data were obtained after the final dose.

trough concentrations on the day prior to and the day of blood sampling as shown in table I. Mean values from the pharmacokinetic analysis of individual subject data are found in table II. Computed by the trapezoidal method, the *relative* bioavailability of the controlled release preparation compared favourably with that of the solution. That is, when the amount of morphine reaching the plasma when dosed with morphine sulphate solution (MSS) was defined as 100%, ($AUC_{MSS}/AUC_{MSS} \times 100$), after adjustments for dosage the relative bioavailability of controlled release morphine sulphate (MSC) was 86%, ($AUC_{MSC}/AUC_{MSS} \times 100$). The AUC was determined for the dosing intervals in order to compare both preparations as they exist at steady-state. Attenuation of the peak plasma morphine concentration was noted with the controlled release morphine sulphate, which at double the dose of the solution gave rise to virtually the same C_{max} . The controlled release nature of the tablets was manifest in the 3-fold increase in t_{max}

and 2-fold increase in absorption half-life relative to the solution.

Figure 1 shows the time course of plasma morphine concentrations and confirms the persistence of morphine itself at 24 hours post-dose, albeit at a minimal concentration. The semilogarithmic plot reveals two distinct processes during the elimination phase (I and II, respectively) for both solution and controlled dose. The data were fitted by least squares to obtain estimates of decay half-lives derived from the calculated rate constants as morphine is cleared from the plasma. Both morphine preparations were shown to have a $t_{1/2(I)}$ of about 4 hours corresponding to elimination up to 8 to 10 hours; the secondary decay occurred with a $t_{1/2(II)}$ of about 40 hours. At 24 hours the morphine concentration was approximately 15% of the peak plasma concentration for both solution and controlled-dose, with the secondary decay responsible for clearance from plasma of only a small fraction of the total plasma load of morphine.

Discussion

The results demonstrate the bioavailability of controlled release morphine sulphate relative to the solution. The value found by Hanks should be emphasised; bioavailability does not reflect oral morphine; this is 15 to 70% (Säwe 1981). The release morphine sulphate value Welsh et al. (1981) is 1.3 hours of Hanks. The longer t_{max} for the controlled release compared with 0.77 h

In addition, the attenuation of plasma morphine concentration with controlled release morphine sulphate demonstrated in this study indicates that morphine can be given at one time without risk to spiking morphine plasma concentrations. It has been observed (Hanks et al. 1978) that equal doses of controlled release morphine yield significant differences in morphine concentration-time curves. The controlled release morphine showed biphasic elimination from the first compartment. The elimination half-life was in the usual range given for morphine (Hanks et al. 1978). However, the deeper compartment occurred with a 3-fold increase in half-life. The elimination process has been studied in single-dose studies of 4 to 14 hours and 20 to 40 hours with a transition between the two half-lives occurring at 8 to 10 hours (Niemi et al. 1975). However, at 24 hours the morphine concentration was nearly 15% of the peak concentration, signifying that the elimination phase involves clearance of a substantial fraction of the total plasma load. This may account for the long half-life of methadone. Presumably, differential

Discussion

The results demonstrate the nearly equivalent bioavailability of controlled release morphine sulphate relative to the solution and confirm the 86% value found by Hanks et al. (1980). However, it should be emphasised that the relative bioavailability does not reflect the total bioavailability of oral morphine: this is about 35%, but varies from 15 to 70% (Sawe 1986). The t_{max} for controlled-release morphine sulphate of 2.3 hours was the value Welsh et al. (1983) found, but less than the 3.3 hours of Hanks. The latter group also obtained a longer t_{max} for the solution, namely, 2.9 hours compared with 0.77 hours in this study.

In addition, the attenuation by 50% of the peak plasma morphine concentrations obtainable with controlled release morphine sulphate as demonstrated in this study implies that a greater dose can be given at one time compared to short-acting morphine without risking untoward effects related to spiking morphine plasma concentrations. In fact, it has been observed (Khojasteh et al. 1986) that equal doses of controlled release and short-acting morphine yield significantly fewer side effects for controlled release morphine sulphate. The plasma concentration-time curve for both preparations showed biphasic elimination. The half-life of elimination from the first compartment was within the usual range given for morphine of 2 to 4 hours (Stanski et al. 1978). However, elimination from a deeper compartment occurred with nearly a 10-fold increase in half-life. Of interest, a similar 2-part elimination process has been reported for methadone in single-dose studies with estimated half-lives of 4 to 14 hours and 20 to 50 hours, respectively, with a transition between decay processes occurring at 8 to 10 hours (Nilsson et al. 1982; Verebely et al. 1975). However, the amount of methadone at 24 hours was nearly 50% of the peak plasma concentration, signifying that the slower decay phase involves clearance from plasma of a substantial fraction of the total plasma methadone load. This may account for the importance of the longer half-life of methadone noted in clinical practice. Presumably, differential binding to the tissues

comprising the 2 compartments may account for the difference between morphine and methadone elimination and further explains the accumulation potential of methadone and attendant adverse effects (Berkowitz 1976; Ettinger et al. 1979).

Therapeutic Implications

In summary, while this study showed that greater amounts of morphine sulphate can be given per dose with the controlled release preparation without affecting morphine bioavailability or elimination, the frequency of dosing with the sustained release formulation could only be determined through clinical analgesic studies. In addition, the clinical relevance of the significantly longer t_{max} and absorption half-life of the controlled release tablets compared with the solution need be made relative to analgesic efficacy study data. Such work has shown controlled release morphine sulphate ('MS-Contin') to provide analgesia in chronic cancer pain for 12 hours in the vast majority of patients and for 8 hours in the remainder (Lapin et al. 1985; Meed et al. 1985; Walsh 1985). While the amount of oral morphine required daily is patient dependent, 2 studies have shown mean daily doses near 300mg (Lapin et al. 1985; Meed et al. 1985). For different patient populations, other reports show around 120mg of morphine over 24 hours to provide adequate control of cancer pain (Homesley et al. 1984; Walsh 1985). Thus, cancer pain may be controlled with doses of controlled release morphine sulphate up to 150mg every 12 hours; however, significantly higher or lower amounts may be required by some patients.

Acknowledgements

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of plasma morphine persistence dose, albeit at logarithmic plotting the elimination both solution fitted by least half-lives constants as morphine both morphine $t_{1/2}$ of about 4 up to 8 to 10 with a $t_{1/2}$ of morphine concentration of the peak and concentration responsible small fraction

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The effects of rheumatoid activity on non-steroidal (NSAID) pharmacokinetics have been extensively studied (Verbeeck, 1985). Serum albumin concentrations in disease activity are frequently altered (Ballard, 1985) as a result of increased catabolism of serum albumin concentration of disease activity (Ballard, 1985). The report describes the pharmacokinetics during naproxen to a patient who had diminished and the concentration returned to

Case Report

Classic RA was diagnosed 10 years. She had had joint pain and morning stiffness of the hands. Examination revealed inflammation: subcutaneous